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Interview with Eric Davidson

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Interview with Eric Davidson

By Ute Deichmann.

Eric Davidson was a professor in the Division of Biology at California Institute of Technology, since 1974. He was a leading scientist in the molecular biology of development and its relationship to evolution and the founder of the concept of developmental gene regulatory networks. He died on 1 September 2015 in Pasadena, at the age of 78.

California Institute of Technology, 14 December 2013.

### **1. MBL Woods Hole, U. Penn, Rockefeller Institute - Becoming a molecular biologist of early development**

Ute: I want to start at the very beginning of your scientific biography. I have read that as a high-school pupil you spent some time at Woods Hole Marine Biological Laboratory.

Eric: I went to a very primitive high school, nothing that today would be regarded as acceptable science teaching whatsoever. But there was one wonderful woman whose name was Miss Krum; she probably was educated around 1910. I went to high school in 1950, and I graduated in '54. Miss Krum taught the biology class, which was in 10<sup>th</sup> grade. So that was 1951. She was an elderly lady with grey hair. When I came in on the first day of class, I said, "Miss Krum, I'll make an arrangement with you. I'll make all the laboratory preparations for the whole class, for the whole year, if I don't have to take any examinations except the final." She looked at me and said, "Do you know how to use a microscope, young man?" I said, "Yes, ma'am." Because one of my father's friends had given me that for a Christmas present a few years earlier, I knew a little bit about using a microscope. So she said, "Well, you go home and make some preparations and show them to me tomorrow morning." I took some Paramecium and other stuff and stained them with permanganate, and she said, "Very well, young man." The result of that was that I became completely fascinated with biology, looking at all of these wonderful things that we had to show the class the whole year.

The summer after that, or the summer after that, I forget: My father was a famous painter, as you know. He ran an art school for other artists; for people who wanted to become artists, for adults, not for kids, for ex-army veterans and all kinds of people, right on the property we had. This was in a famous art colony that was called Provincetown at the end of Cape Cod. One of his "students" was a woman who was married to a famous professor of biology who at that time worked at MBL [Marine Biological Laboratory] in the summer. MBL is at the other end of Cape Cod from Provincetown; it is about 70 miles

away. Her name was Ellen Donovan, and she ran a Salon Des Artes in Philadelphia near the University of Pennsylvania, where he taught in the winter. So through her, it was arranged that I could work in the laboratory of the famous professor for that summer at MBL. I had just turned 16 and I had a car. So I could drive back and forth on weekends. I had a girlfriend down in Provincetown and I would spend the whole week at Woods Hole. And I was supposed to wash laboratory glassware just to be around the laboratory. But it was a practicing research lab, and as soon as I walked in, “Boss”, as he was called - his name was Professor L.V. Heilbrunn and he was a then-famous, leading figure in an area which has totally disappeared, called “cell physiology” – there is no such thing anymore - said, “If you’re going to be in my laboratory, you’re going to do research.”

Ute: Not washing the...

Eric: AND wash dishes. You wash dishes at night.

So I said, “What am I going to do the research on?” He said, “I have a good problem for you.” He was very interested, presciently, long before anybody realized he was right, in the concept that many aspects of cytoplasmic function are mediated by calcium ions, which turned out to be completely true. We now know how and why, and the many pathways that calcium affects. So he thought that many, many things depended on calcium, though he was focused on the phenomenon rather than the mechanism. And the particular problem I had, was to determine whether calcium had anything to do with the cellular clot that sand dollar [an echinoderm related to sea-urchins] blood makes if the animal is injured. So when our blood clots, we have platelets that break down and fibrous protein emerges and makes a clot; it’s largely a protein clot. With these animals, what happens is that the cells themselves change their form and form a kind of cellular mat within minutes.

So I started working on this problem. The cells extrude long actin filaments which mesh with each other to form the cellular clot. Just as good a blood clot, by the way, as we make. It happens very fast and works very well. My job was to find out whether this clotting reaction depended on calcium. I had to chelate or trap the calcium chemically and figure out a clotting assay in vitro. Anyway, it worked out fabulously. So I did this research. And if you look, in fact, you’ll see that my first publication was dated 1954. That was when I had to give an account at the annual MBL Society meeting about my summer research, just like all the other summer researchers, and I was a 16 year old kid. If I had known who was in that audience I would have fallen down between the cracks in the floor of the theater, because some of the great names of early 20<sup>th</sup> century embryology were out there. E.G. Conklin was in that audience and a number of other such people. So there were many old-timers there, whose work I later reviewed in my 1968 book. So I grew up in an environment of classical embryology. And I went back to

Woods Hole in subsequent summers. So it was August 1953, and Heilbrunn said, “You’ll publish this abstract”, and that’s my first publication (1954).

They had, in those days, something called a Westinghouse Science Talent Search. Every year they had this nationwide competition for high school kids that did research in any area of science. And you had to have a research project that you had done, and you had to take a really difficult examination. The examination was sort of mathematical and logic based. It wasn’t memory; it was a brain examination. They chose 40 winners from the whole country and they got a trip to Washington and so forth. It was so prestigious that most universities would give any one of those people free tuition to university. I was one of the 40 winners that year.

Ute: 1954?

Eric: Yes it was 1954.

That meant I could go to college without worrying about tuition, because my father at that time didn’t have too much money at all. The only place that wouldn’t let me in with a scholarship was Harvard, because they said that my scholastic aptitude examination results indicated that I could never become a scientist. They turned out to be wrong.

I had my revenge four years later when people were trying to get me to graduate school, particularly Harvard. I said, “Four years ago you said I wasn’t good enough to come to Harvard so I am not coming now!”

One thing led to another, and so I got to go to the University of Pennsylvania, where I worked in the laboratory of Heilbrunn, the same guy who started me off at MBL. By the time I got out of there I don’t think I had gotten too much college education, but I certainly knew my way around a laboratory. I was author and co-author of several more papers and those years of work in his laboratory gave me a great start for graduate school.

Every afternoon I talked about history of science, embryology, cell physiology - I was into Boverian embryology from that time on. But Heilbrunn had terrible relations with the nascent molecular biology of the time. He used to call people who did that sort of thing, “the grind and find boys.” But in my last year, he said, “Go take this course in molecular biology that ‘so and so’ gives”, and I only later discovered that “so and so” was his worst enemy inside the university, but he wanted me to take his course anyway.

Then I said, “For graduate school I want to stay with you, boss.” He replied, “You know everything I could ever teach you,” and he said, “you’re going to go to Rockefeller and study nucleic acids with Alfred Mirsky.” I said, “what?” I had never heard of Mirsky. It was completely shocking that despite all the stuff he was always saying about this, he

knew in his heart where the future was, and he knew that's where I had to go. And so that's where I went.

Rockefeller had just started its graduate program. It was hard to get into; you had to have something supposedly special or you wouldn't get in there. But fortunately they let me in. I had a fast start and just came from nowhere; from completely nowhere. Then of course, I found myself in the temple of molecular biology; there are other stories after that. That's how I started.

Ute: So the next person who had a strong influence on you was certainly Mirsky. Was he responsible for your entering molecular biology?

Eric: Not really. In a way, yes, and in a way, no. I should say that while I was at the University of Pennsylvania, almost every afternoon I had one of the most unusual experiences a student could have. As I mentioned, my boss L.V. Heilbrunn would take me into his office, and as the sun set over West Philadelphia, we would talk about the history of science. And we would talk about embryology. And we would talk about the discovery of the cell. And we would talk about all the people that he had known. And my honors thesis was Chapter 14 of E.B. Wilson's "The Cell in Development and Heredity", the crowning glory of Wilson's Third Edition, where he synthesized everything together. So I was thoroughly oriented towards the problem of mechanism in embryonic development. I knew everything anybody had done in embryos from a classical point of view, right from those days after my start at MBL, which was still pervaded with the scent of cell lineage studies; they were still going on when I went to the Rockefeller Institute. That's where that interest really came from.

Mirsky was, of course, a very different sort. He was a real scientist as opposed to a person who describes things. Although Heilbrunn did experiments too, Mirsky was more experimental than he. He was not just an observer at all. It was all about experiments and I was a pretty good experimentalist thanks to Heilbrunn. Mirsky brought into my life quantitation, physical chemistry, mechanistic molecular biology, and I've always had those two strains of scientific orientation. Hard nuts mechanistic stuff applied to the most interesting question in the world to me, which is how embryos develop.

Mirsky also talked a great deal with me every day. And so from his point of view – the same as mine – it was completely absurd to think of anything else in science except how things work .... He was interested in differentiation as opposed to embryogenesis per se. Thus, when I came into that lab he was very busy arguing for a theory of cell differentiation that he called "variable gene activity" which depended on regulation of gene activity, and he was completely clear-headed about that. He was also completely correct. So everything about differentiation depended on regulating genes, in his mind. But making an embryo isn't differentiation; it's a lot more complicated than making a

cell differentiate. Also going on in Mirsky's lab at that time were the initial experiments on histones and how they interact with DNA. I learned a lot of DNA physical chemistry too. So DNA was my house, and my mind was on development.

Ute: Mirsky was one of Avery's strong opponents after Avery demonstrated that DNA is probably the sole material of the genes ...

Eric: Yes, but you're talking about a different time.

Ute: My question is, did Mirsky later on accept prokaryote molecular biology such as Avery's?

Eric: He accepted it when he became convinced that DNA was the genetic material in animals, and I think he really accepted that only when he and Vendrely did those genome size measurements - in 1948 they published them - in which they showed with great precision that diploid cells have exactly twice as much DNA as haploid sperm. And he used that argument to say that this can only mean that DNA is the genetic material, because he knew about meiosis. And that nothing else could be distributed like that. It was down to decimal point accuracy because the measurements were very good. They took blood cells, for instance, in frogs and fish which have blood cells that contain nuclei, unlike us, and compared their DNA content to that of counted sperm. They measured the DNA content not just spectrophotometrically but with chemical methods. Not just by staining cells, but by measuring molecular mass like a chemist would; Mirsky was originally a chemist.

Ute: Which other scientists were influential for you at the Rockefeller Institute at that time?

Eric: There was a guy named Ted Shedlowsky who was a physical chemist. I enjoyed talking to him very much. But it was a period when laboratories at Rockefeller were extremely insular. They were all major figures, sort of like this place [Caltech] when I came here. Everybody was in the National Academy of Sciences even though the faculty wasn't that large. They all were, or thought they were, great men - no women of course.

Ute: Here, or over there?

Eric: There, at Rockefeller. I didn't actually have a great deal of scientific input, I don't think, from anybody there except Mirsky. I mean, I learned a lot of stuff; I learned some physical chemistry from Shedlowsky, who has died now. And Norton Zinder was there and did viruses. There were a number of people, but I wasn't close to any of them. I didn't care for Rockefeller very much because it was very stuffy and everybody wore a suit and coat every day. And I was riding motorcycles into work in jeans and a black leather jacket...

Ute: Motorcycles in New York?

Eric: Yes.

Ute: Wasn't it suicidal?

Eric: No, it was good! I was a good rider. When I came here to California, for 25 years I never had a car, I just rode motorcycles.

Ute: It was at Rockefeller that you proposed, in '69, together with Roy Britten from the Carnegie Institution in Washington, the hypothesis of gene regulation in higher animals...

Eric: That was a long time after - I got my degree at Penn in '58 and then did my Ph.D. at Rockefeller in '63. For my thesis I worked on something that was completely unique in that laboratory. It was a problem, we would say today, in gene expression dynamics. The question was, "what is the timeline between expression of a gene in a differentiated cell and the appearance of a differentiated function in the cell?" I made a cell line that was differentiated because it made a specific biochemical molecule, a hyaluronic acid assay. These cells made that stuff quite actively in culture. It was at a time when actinomycin appeared as a drug that intercalates in DNA and prevents transcription. I blocked transcription and measured hyaluronic acid synthesis kinetics, which depended on the prior synthesis of an enzyme. So it is a differentiated cell function. You shut the gene down and within 20 minutes the synthesis of hyaluronic acid started to decline. Which meant there is a very immediate relation between what the genes were doing and the differentiated functions in the cell. I called it the immediacy of gene control. That's how I did my thesis. You can see what I was thinking – it was all about how genes have to be controlling all these differential cell functions.

Right after that, I dropped all of that and went into early development of embryos. At that time, Mirsky kept me on as sort of a research member of his lab – we don't have this situation any more in academia, this is like a mid-century European arrangement where the lab head was actually the department head and he had a variety of people that could work in that department, sort of partially independently, on his funds, or on whatever they could get.

## **2. Work on gene regulation in higher organisms**

Eric: I actually got a grant almost immediately from the American Cancer Society. That first grant was about the proposition – I still remember the first sentence of that grant application, which was that, "The egg is like a can of gene regulatory factors." I knew so much traditional embryology and I knew that there were a lot of embryos unlike

Drosophila or frog embryos, such as those many marine embryos where the cleavage planes canonically divide the egg up into different cells and the cells have different fates, different differentiated fates, the same in every embryo of the species. So how could that be? I thought that the molecules that regulate those genes, whatever they are, have to be asymmetrically distributed according to that cell lineage pattern. Ergo, the egg must contain gene regulatory molecules in order for them to be divided up by cleavage. So that's what it was about. That's where it started. That led to thinking about how gene regulation could really work from that point of view.

Ute: There was, of course, already the model of Jacob and Monod. [the operon model of gene regulation in *E. coli*, 1961].

Eric: For me, bacteria were so different from animals. One gene doesn't make a differentiated cell type; that was obvious to me. It had to be some kind of a system for sets of genes being able to control cell fates. And that's what the Britten-Davidson model was attempting – using what logic we knew.

Ute: You were convinced that the operon model wouldn't work with eukaryotes?

Eric: You know, I didn't even pay attention, to tell you the truth. I read it ...

Ute: But how is it that everybody talked about the operon model, and the model was so wonderful and functioning in the ...

Eric: I read it, but it didn't penetrate. I used to discuss it. As I recall, everything they did was about repression.

Ute: And you said it is just the other way around.

Eric: So we have a problem; we have to activate genes. For me, bacteria were so entirely different from animals in terms of their genomes - I already knew because I grew up in a laboratory that was interested in genome size, that *E. coli* has 5000 genes - a minute genome instead of a genome 1000 times larger with so many more genes; we didn't know how many. We knew that there were all kinds of RNAs that bacteria didn't make. And nuclear RNA had been discovered, but nobody knew what it did. So the relevance of the Jacob & Monod ideas was definitely not obvious to me. I really didn't pay any attention to it at all, to tell you the truth, until years later. That was something that Michel Morange figured out and he was exactly right.

Ute: Which animals was the paper with Britten based on? Or was it a purely theoretical paper?

Eric: It was completely theoretical. It's called, "A Theory for Gene Regulation in Higher Cells". It took some evidence from *Drosophila* and some evidence from this and some



evidence from that. Remember, I'd already written my '68 book by now. In that book are some of the ideas that were formulated in the paper with Britten.

Ute: I don't know anybody who is so strongly convinced as you – or had been convinced early on - of the genetic determination of development.

Eric: Boveri certainly was.

Ute: Yes, in the end he was, but later on, this idea...

Eric: And Wilson really was too, although he was careful...

Ute: Wilson and Boveri; it was also a time when DNA already played a strong role as a possible candidate for the material basis of the gene. But all of that went down shortly afterwards. And the embryologists did not...

Eric: It went down and causality in embryonic development disappeared totally. It was pushed and pulled. I could discourse on that history for you as long as you'd like. It's a different question.

Ute: No, that is not what I want to talk about now. I want to know why you were so convinced of this basic idea from an early stage.

Eric: The logic was obvious. It still is. Development is a species-specific character. What else do we inherit in the sperm except DNA and some packaging proteins, for example?

Ute: Generations of biologists believed in the determination of development by the cytoplasm. But you did not. They also had their logic.

Eric: Yes, mitochondria, right. But by this time we knew that the only DNA to speak of, except for very simple DNA like there is in mitochondria, is in the cell nucleus. This is where all the complexity is. It was completely clear from the work of the Boveri-Wilson school that the process of development is controlled, as it goes, at every step. The German geneticists who advocated cytoplasmic inheritance, to the contrary, they just didn't think straight. And then the embryologists - they wanted to do embryos without nuclei.

Ute: Yes, they just focused on the cytoplasm.

Eric: They just didn't care about anything conceptual in my opinion, only phenomenology. They could not even begin to think about causality. Because for them, causality was if you stick a second head on the other side of the egg and you get a second tail going. That's what they call causality. But if you're interested in mechanisms, you just had to try to knit together what we knew already about how DNA makes messenger RNA, makes proteins, how organisms are different one from another, how they have to

have a program for development. That has never changed. Everybody knows that now. I never understood why to people of these huge schools it wasn't obvious. There was also a very strong anti-theoretical trend.

Ute: In embryology?

Eric: Yes, particularly in British embryology. Very strong. “Don’t tell me any ideas or generalizations about what you do; just tell me about your experiment. That’s all I want to know.”

Ute: The influences of positivism?

Eric: Positivism—this is something you know better than I—was not inconsistent with any theories. This was hyper-empiricism, that is what it really was. On the continent the opposite was true, with all kinds of crazy theories that had no basis in reality. Like cytoplasmic inheritance determining the properties of the organism.

Ute: Yes, the properties of higher level taxonomic properties.

Eric: Yes, upper level taxonomic properties, correct. But if you think about it, the proteins have to be made – one cell makes different proteins than another – somebody has to control that. That’s the regulatory system – that system controls what the cells become. What the cells become where, determines how the embryo develops, determines everything. So how are you going to think about it any other way if you actually want to think about it mechanistically? Right from scratch.

I think that the Britten-Davidson model was just a simple application of logic. It was at least based on what we knew about what embryos actually do. And it included the idea of how signals would work. In many ways that actually is one of the things in that model that was the most, may I say, prescient and predictive of what we found out later. We had in that model gene regulatory proteins, a special function which was to receive signals from other cells and then alter them, the result of which would be to cause the expression of other regulatory genes, which is exactly what happens in inductive signaling. That makes development work. You think, “the signal changes the fate of the cells. Well, how can that happen?” It must mean that other genes have to be expressed in response to the signal. Which much mean that other gene regulatory molecules have to make those other genes be expressed. And so there must be these parts of the system. And there are.

The paper had a big counter-factual aspect to it, because we thought that there are two kinds of molecules that can recognize DNA sequences. It had to be something that recognizes and reads DNA sequence. That model was all about regulatory DNA sequence, which is what makes the whole system operate. But you could read a regulatory DNA sequence with proteins or with RNA. We built that model on RNA

reading the sequences because it was simpler to deal with complementarity than with what was completely unknown, namely how proteins can read DNA sequences. Although there was evidence that they could.

It was known that some proteins bind to DNA, and we knew about viral proteins that read DNA sequences. In the '71 application of that model to evolution we said it could be either RNA or protein, but the logic is going to be the same. And the logic is the same, but the first model was basically built on RNA recognition. Well, now it turns out that there are a number of regulatory functions that do use complementary sequence recognition by regulatory RNAs. But the main heavy lifting of regulation is done by protein - DNA interaction, of the kind that had already been found in bacteria. I suppose if I had paid more attention to Jacob and Monod we probably would not have built the model using regulatory RNA. We discussed whether we were going to talk about protein or RNA, and RNA was neater and easier to deal with because of natural complementarity. But that was wrong, from the standpoint of how it works. The logic, however, was just exactly on the beam.

For many years we couldn't really work on the model, because we couldn't study this. In the '90s I decided that now is the time to go back to what I'm really interested in. The place to start thinking about it, despite ALL that had been discovered, was that model. Because I had started thinking about it from a systems point of view.

By then, we knew from *Drosophila* there are developmentally essential regulatory genes. A lot of information showed the right way at a microscopic level of protein - DNA interaction affecting transcription. But there was still nothing about the global architecture of the regulatory system. And that's what that 1969 model was about, so that's where we had to start again.

It's a funny thing. In '97 I wrote a paper with a post-doc, Maria Ina Arnone, on what real gene regulatory networks for development were going to look like. If you look at this first post-interregnum paper - using the word interregnum for the space when I wasn't working on regulatory systems for development - it looked remarkably like that '69 architecture, and it was constructed on what we could deduce from current knowledge then. By that time there was a lot of cis-regulatory stuff. But still, there it was. And that's when I decided, now we have to find the gene regulatory network and show everybody what it does in fact look like, the real thing.

Ute: In '71 you left the Rockefeller Institute and moved to Caltech where you became associate professor and then full professor.

Eric: Well I did not get along very well at Rockefeller in those years after my degree – I stayed at Rockefeller with Mirsky. But Mirsky got very ill, and he became

psychologically unstable. He had what today would be completely curable. It was bleeding ulcers. But the hemorrhages that occurred were so severe that the effects were almost drowning. Anoxia impairs survival of the brain cells; they're the most sensitive to anoxia. And so he got more and more paranoid and he started to fight with absolutely everybody at his place, one after the other. Everybody became his enemy. I was the last one to go, but me too. Then things really began to go to hell. I moved out of his laboratory and I had no place to go. I worked as a guest in another's guy's laboratory who was a friend of mine. I got a little bench. Then Rockefeller considered me for tenure but decided that I couldn't get tenure, that I was not good enough.

So I was considering doing other things. Somebody offered me a lot of money to set up a laboratory with running sea water to do lobster genetics for commercial purposes, because I was already good with marine organisms. I almost did that. But about that time, Caltech discovered that I was on the loose. My predecessor here was Albert Tyler, who was a sea urchin developmental biologist. He did basically nothing most of his life, until the last few years when he was one of the discoverers of maternal messenger RNA.

He used to play in the softball game they had every year with the professors against the students, and he had a heart attack on the baseball field and died. So they wanted to replace him. They first offered the job to Walter Gehring, who refused. And then they offered it to me, who accepted. So I was their second choice.

### **3. Caltech; sea urchins; Max Delbrück; disputes on evolution**

Ute: Did you start to work with sea urchins only then?

Eric: Yes, only then. But I already was working with marine snails, an animal that I was familiar with from my boyhood at Cape Cod. That was one of the most wonderful animals for determinant cleavage. I published a paper on that in '65, actually. Wilson knew about this animal because one of his students discovered an interesting phenomenon in it in about 1904. At the two-cell stage it extrudes cytoplasm in one of these cells, which is connected to the cell body by only a thin strand, so that the cleavage plane doesn't have to go through this huge, big mess of cytoplasm. It just sticks it out in a lobe. And then after it cleaves, the cytoplasm goes back into one cell. So you have a little cell and a big cell. And then it does the same thing in the next cleavage. A number of animals do this. Wilson's student discovered that at the point where it is only connected by a thin strand of cytoplasm, you could easily get that piece of cytoplasm off. Though no nucleus is removed with it, when you grew up those embryos which lacked the cytoplasm of that lobe, certain parts of the embryonic body never formed. It would never make a heart.

Ute: When you grew up the ones with the nucleus, or the other?

Eric: Well the other one can't grow. The nuclei are all there, there is no change in genetic material, but a specific element of cytoplasm has been removed. So it was the perfect case for me of cytoplasmic gene regulatory molecules which would cause this cell to transcribe some genes the other cells didn't. That was the theory. But no one has yet isolated the gene regulatory molecules in that lobe, and it's hard to work with because you have to do everything by hand with forceps. But we studied it, we studied the transcription profiles: When you take that cytoplasmic lobe off, the transcription profile of the remaining cell changes right away. In the course of that, I discovered how to make those animals think that it was winter when it wasn't, by changing the light and temperature conditions so we could get eggs all year round. So that stood me in good stead. When we did the same thing to the sea urchin system, it worked well.

My work with sea urchins at Caltech was in molecular biology. The reason I went into it was because you could get clean RNA and DNA out of it. It was comparatively hard to get that out of frogs or anything else. But to get DNA and RNA and polysomes and ribosomes and mRNA, anything you wanted, it was already clear you could use sea urchins for this better than anything else. And I just knew that that was where the future was going to lie. And I was completely, as usual, in a different frame of mind than everybody else, as they all thought genetics would solve the problem while for me it had to be nucleic acid molecular biology.

Ute: So you took over the sea urchins of Albert Tyler knowing that it would be ...

Eric: Well, there were other people, not Tyler. But Tyler had been working on that. I did what I did independently of Tyler, but I looked around deliberately for what's the organism that's going to make this possible.

Ute: Boveri also worked on sea urchins, among other animals.

Eric: Absolutely, and I was certainly impressed with that.

Ute: It's really interesting how long-lasting an effect this had.

Eric: Yes, because it worked, what he did.

Ute: When did you learn the chemistry? Biochemistry?

Eric: We've done everything in my lab over the years, whatever it takes – molecular biology, biochemistry, physical chemistry – we do it all. Cell biology.

Ute: Also, you said you did it already with Mirsky.

Eric: Yes, I grew up doing that stuff. Made nuclei, made proteins, later made clones; DNA renaturation kinetics, RNA hybridization kinetics, transcription kinetics. It was a wonderful partnership with Roy Britten who was tuned into kinetics from the start.

Ute: At Caltech, Delbrück was still around, right?

Eric: Delbrück was the biggest influence I had. He was quite a character, I can tell you that. Max had the room right across the hall from my office. I saw him every day when I came here. He was my closest neighbor and I had more interaction with him than anybody else, I think.

And then I started working with Roy Britten who, like Max, was an ex-physicist. These guys had a lot of influence on me. They were both mentally extremely tough. And “they suffered fools not lightly”, as we say. They provided my greatest experience, I think, of all ... I’ll just tell you two little stories about Max.

I would go in his office and he’d say, “What came out in the literature this week that’s interesting?” So I’d say, “Did you see that paper in Science on such and so forth?” He said, “I don’t read Science.” I said, “How can you not read, Max?” He said, “I depend on you to tell me if something’s interesting. Why should I read?”

One day we got into a big argument about DNA renaturation kinetics, which I don’t think he believed in, although one of the founders of it was his colleague, Norman Davidson, who was here. And they’d been colleagues already for a decade or more. After some kinetic argument Max says, “You don’t know any mathematics.” I said, “OK, Max, get somebody to teach it to me then.” The next day one of his senior post-docs arrives in my office with a bunch of mathematics books under his arm, and says, “Max tells me I’m supposed to give you a course in advanced mathematics.” I said, “OK, let’s start.” So he did and I did. And so for a whole year I did problems and we went through every damned thing you could imagine. And that was one of the most useful things I’ve ever had. I mean, I was already an associate professor here. But that was just great. And about half of what we went through I’ve used, ever since, in my scientific life. Half of it I never looked at again. But that really made everything that had to do with calculus, which I’ve used a great deal since, just like child’s play thereafter. I mean, I’m not very fast at solving differential equations but you don’t have to do them anymore. The computer does it. You just have to set it up and understand it. And that was just wonderful.

So that potentiated the next phase of a lot of the work we did, which was on transcription kinetics. Britten and I wrote the book on complexity and RNA/DNA transcription rates and turnovers, and synthesis rates, and decay rates. Thus the sea urchin became extremely well described at a quantitative molecular biology point of view. Compared to any other

embryonic system, it was like tissue culture cells for the rest of the world. Way beyond anything else.

As a famous *Drosophila* geneticist once said to me - I put all this in the third edition of my *Gene Activity and Early Development* - "That book is everything you don't want to know about development," all that quantitative molecular biology. What you want to know is which genes made bristles curl, or make fly eyes narrower." Later he apologized to me for that. Many years later.

It was, in fact, everything you do want to know about development. And it's all come home to roost since the rise of genomics and systems biology. All those measurements turned out to be enormously useful.

Max himself worked on the most intractable organism you could imagine, and never got anywhere with it. The field has almost totally died after he stopped working, after he died.

Ute: You are talking about his *Phycomyces* work?

Eric: Yes, it was completely intractable. It led nowhere. But he understood everything. It was said he had a luminous mind when it came to processing information. But he had every possible classical weakness of the physicist in biology. Although he'd been in biology for decades by then, he still just didn't know what was going on or anything about how animal cells really work.

But he was a joy to talk to. I talked to him every other day.

Ute: He had a romantic mind, didn't he? He was influenced by Niels Bohr.

Eric: He liked ideas, if that's what you mean. He was the opposite of the hyper-empiricist, let's put it that way. He liked that idea that you could have an idea; that ideas are important in science. And I like that idea too.

Ute: He for a long time didn't believe that the riddle of gene replication would be solved at the biochemical level.

Eric: You have to be careful about that - I mean, people's beliefs always change with time. Just like when I knew Mirsky, it was long after the discussion about transformation principles in the '40s. When I knew Max, it was long after the days when DNA replication was disputed. You're talking about '50s arguments. By the 1970s that was all a dead letter, that whole discussion. People knew how DNA synthesis worked.

A lot of Max' early thoughts were particularly naïve, about thermodynamics and biology. He had dropped all that stuff by the time I knew him.

Ute: But he created genetic phage research and that was very important.

Eric: That was very important – a long time earlier. Then he wrote a book which made it apparent that if it hadn't been for what happened in those few years there wouldn't be any biology. It was couched as an autobiographical triumph of Max, which was also not very historically up to date. It was complete nonsense, that book. But I forgave him all of that hubris and all the rest of the silliness, which other people certainly did not. I liked him a great deal.

And he was incredibly rude. He was famous for going to a seminar – going to every seminar – and if the seminar speaker didn't explain what the seminar was about, what the problem was, what the approach was going to be in intellectually clear terms within the first ten minutes, he would extremely loudly get up, snort, and stomp out of the room. So of course as soon as anybody young came here they were terrified that Max was going to get up and leave.

Ute: Yes, he was known for this kind of thing. At the Institute of Genetics in Köln, which he co-founded, he would read a newspaper when he found a lecture boring or the speaker did not get to the point. One day one of his students, Fritz Melchers, put newspapers on the chairs outside the lecture hall where Max would give a talk.

Eric: You mean all of his students started reading the newspaper when he was talking?

Ute: Yes, everybody understood and took a newspaper, went in and Max gave the lecture. And after a while, one after the other, they opened their newspapers. And Max was SO angry! He said, "If you don't put the newspapers away, I will go."

Eric: So I liked Max very much, but not too many years after I got here, he got multiple myeloma and died. I knew him in the final period of his life. He was still leading these big trips out in the desert. He insisted that everybody in the faculty, if possible, would go and camp in the desert. I didn't like group activities, so I never went.

He was very teutonic in his behavior patterns. He would sort of bark and stomp around.

Ute: He came from an aristocratic family. But his father had dropped the "von".

Eric: I read his father's book, by the way. Did you ever read it?

Ute: No, I didn't. He was a historian.

Eric: He was a Roman military historian. One of the worst books, I ever read. It was completely boring and also not very correct, by the way. But, of course, he was writing at a time when people knew a lot less. He just quoted classical authors and didn't make any



use of archaeology or anything new whatsoever. It was completely scholastic and stuffy. It was redolent of an old-fashioned university department.

Ute: Coming back to your work. Another characteristic about you as a molecular embryologist is that you extended this research to questions of evolution. When did you become interested in evolution?

Eric: That goes right back to the days of the Britten-Davidson model. If you look at the *Quarterly Review of Biology* article that we wrote on evolution (1971), you'll find there the first statement that says extremely clearly and explicitly that if you want to understand evolution, you have to understand the change in genomic programs that control development. That's the only way to consider it. Therefore it has to be concerned with change in the architecture of, what we would call today, gene networks. We said it straight out, clear as day.

Ute: But how did you arrive at this conclusion?

Eric: Since the body plans are made by development, when you consider evolution of different kinds of animals, it means their developmental process is different. How else can you think about it? Darwinian evolution was of a completely different kind. It was all about small changes and they felt if you could understand changes in petunia colors, you could understand changes in whether animals have heads or not. And that's just total nonsense. But you can't really blame the Darwinians, because all of Darwinian theory, from the Neo-Darwinian synthesis of the 1930s, was built in the absence of, and ignorance of, any knowledge of how development actually works. Other than wrong theoretical ideas. And in the absence of any knowledge about how transcription works and in the absence of any knowledge about anything that has to do with how the processes of life that make animals actually occur. So it couldn't possibly have been right, and it wasn't.

Ute: But the problem is that neo-Darwinians did not include the growing knowledge about development later on.

Eric: Now, that's what I was going to say. Where you can fault them is that they didn't learn. That they stuck their heads in the sand, and ever since they have been like ducks with their heads stuck in the sand. So it's been necessary to start over again, considering the nature of evolutionary process. It has pervaded every aspect of evolution. How do we interpret the fossil record? What happened? How do we interpret the real-time changes in rates of evolution? And that's a very lively field when you think about it properly, as you'll see when you read chapter 7 of our current book, which is all about this.

That chapter is done, but the book isn't. We're in the last chapter.

Ute: Because of your criticism of neo-Darwinism, some people from Intelligent Design or creationism embrace you. How do you deal with that? Do you react at all, or do you just let them go?

Eric: There are three classes of people I never talk to. I don't talk about religion, I don't talk about neo-Darwinism, and I don't talk to Republicans, I mean, extreme Republicans – Tea Party Republicans. They're all the same to me. They all live in a counter-factual world, and I don't deal with them. They all believe in "belief-based" decision-making and I don't care for that. They live in an irrational world, all three groups of people, so I don't deal with them.

Ute: You include neo-Darwinists in that group?

Eric: They're just wrong. They're not irrational, they just refuse to learn.

I absolutely refuse to debate or discuss with Intelligent Design people. And I've been asked to often; I just won't do it. Now it is also true that I have refused, and will continue to refuse, to debate with neo-Darwinians about whether protein evolution or regulatory evolution is more important; I can't waste my time doing that either. They are hopeless. Like Jerry Coyne. I have often refused to get into a discussion with him, and I just won't do it; it's a total waste of time.

#### **4. Gene Regulatory Networks; Disputes on genomic determination**

Ute: I would like to come back to the gene regulatory networks. In your model, you transformed, together with Peter and Faure, the GRN model into a predictive dynamic Boolean computational model, and you were able to confirm the predictions experimentally. This is certainly the first time that such a model was constructed in developmental genetics. What are the responses so far?

Eric: If you talk to people that care about this, they say it's such a landmark. If you talk to developmental biologists, they say, "what does this have to do with what we're interested in?" I mean embryologists. I think my interests are more epistemological than many of my colleagues and always have been. The same with Isabel Peter. She has the same kind of argument in her mind.

If you're interested in the ideological framework, it is based in the genome. Because that's where the information is. And so there is a fascinating world of logic and mechanism that originates in the program of the genome. I'm not talking about encoding proteins; I'm talking about how the shape of the regulatory network modules determines

its function. The characteristics of that are fascinating. That's what I've always been interested in – what's the shape of the regulatory control system?

Ute: By shape you mean...

Eric: How does the topology, when you draw it out, determine its function. From topological models to Boolean logic models is a direct transition, which gives you the opportunity to make an experimental test of a logic system. Topological models grow immediately out of what's in the cis-regulatory modules of the genome. And what we can infer is done by playing with their inputs and outputs, which is how we solve networks.

Ute: In the end, you test the model experimentally?

Eric: Yes, we can compare the predictions with what we see. What that showed was that the information encompassed in that network model suffices to explain the regulatory changes in state and spatial regulation, which is downstream of regulatory functions in development. It doesn't mean we know everything about how every gene in the embryo is controlled, because we're just talking about the parts of the system that make the regulatory state, which controls everything else. The linkages between regulatory state and function of, for example, hair genes or muscle genes, no-one has solved that problem on a large scale. It can be solved, it's just work.

Ute: At our last conference [at Ben-Gurion University, May 2013], some of your colleagues said that not in all organisms does development seem to be as hard-wired as in sea urchins.

Eric: Yes, well they're wrong. Just show me another organism that doesn't develop exactly the same way every member of the species.

Ute: Do you think that it just wasn't yet really checked?

Eric: We don't know how it works, but just the fact that they come out the same way tells you something, doesn't it? How else can that work? Accident? Probabilistically?

I was talking to Mike Elowitz the other day, and he says, "do you run into a lot of probabilistic bi-stable states?" I said, "Do you think that whether you have a head or not is a probabilistic function?"

Ute: But he deals with probabilistic events.

Eric: In post-embryonic development, in cells where 2/3 become macrophages and 1/3 become some other kind of immune cell, then that can be shifted one way or the other by certain kinds of wiring but – it's not like making a head. You've got to make a head if you're an embryo and every animal has a head.

It's true, we don't know about it in other organisms, but nobody would say it's not that way in *Drosophila*. "Oh, well *Drosophila* and sea urchins are different." Yes, they're different, they happen to be the things we know about. That's what makes them different.

Ute: Gary Felsenfeld showed that changes in chromatin structure, like histone modifications, are important mechanisms of development. Do those changes in chromatin structure play a role in the development of the sea urchin?

Eric: As Gary was the first to tell you, these kinds of change occur downstream of regulatory interactions with DNA. But almost everything we know about that pertains to post-embryonic functions. Or late embryonic development, where there is a long preceding history in the cells on which the observation is made. In other words, they're already differentiated as mesoderm cells; they're already differentiated as blood cells. It's completely unclear, at this point, if many of the aspects that show up in analyses of the importance of chromatin structure pertain also to what happens in the first hours or days of a rapidly developing animal, where there is yet no prior history.

I think one aspect of it that's sure to be true throughout, is what happens in repression. This business about remembering cell fate through chromatin structure seems overblown and overemphasized in importance. A lot of what these people talk about is what they call epigenetic memory, which I think is overemphasized. Much of development doesn't involve any processes in which cells have to do that. And where it does happen, I think that initiation of those states is not the same thing as the transferal of those states to daughter cells once they're initiated. Development is about the initiation of new regulatory states, mainly. I think that the one part of that whole area that is relevant to all aspects of developmental gene regulation, early and late, is repression. Repression involves a series of irreversible downstream processes that end in the shutting down of specific locations in the genome. And that, I think, is true in early development and every other kind of development. All we look at is the fact that the gene is shut off. Now, if you want to ask what happens to it ten hours later, you'd probably see the same thing in a sea urchin as in anywhere else. But we don't look at the mechanism; we don't care, as long as the gene is silent.

Ute: You are one of a number of researchers who have publicly warned against the far-reaching generalizations of epigenetics. For example, against the argument in *Nature*, that epigenetics and not genomic differences explains how the diversity of life came about.

Eric: That is completely and utterly nonsensical. It's an anti-genetic argument.

Ute: Why do you consider these tendencies dangerous and not just erroneous?

Eric: Because they take the discussion away from where all the causality exists, which is in the genome. Once you get away from causality, then we are back in the world of

irrational argument. “You too can be free from being enslaved by your genes. Just don’t eat so much fat.” This is what it’s about. You have magazine titles like that.

I think it is dangerous because there is a longstanding, latent, visceral dislike, in the uneducated mind, for the idea that the genome actually determines things. And it’s partly because of the hangover, the stupid exaggerations of what the genome does from the first half of the twentieth century. Eugenic ideas that the genome controls intelligence and personality and blah, blah, blah. We still don’t know very much at all about the genomic basis of mental functions, and so as long as there’s an area of ignorance, then it can always be filled with nonsense. But now we have some areas where we don’t have ignorance – we understand what’s going on. And so instead of saying, “well, that’s an exception”, you’d better do the intelligent thing and say, “here’s one of the few places where we really understand it. Let’s assume that this is the way the process works, because this is the way it does work here, where we know something about it”. And so you’d better think about the other processes in the same terms

Ute: Are you afraid that these tendencies will affect science and science funding?

Eric: I’m not talking about funding, but I’m talking about attitudes that result in really poisonous thoughts, for example, “I don’t believe in evolution” or “I don’t believe that genes control what happens.” Those are poisonous thoughts; they’re poisonous because they lead to fundamentally counter-real attitudes. Which means that no one can think straight about the world they live in. One of the most important aspects that we’ve learned in all of biology is that the regulatory information system encoded in the genomic DNA of animals is what determines what we are in terms of our body plans and therefore much of what we can do with each part of our body. Now, of course, part of what we can do is respond to experience, that’s not genetic. The capability of doing it is genetic, but not what happens. Not beginning there means you don’t understand anything about the nature of yourself or of other animals. Anything. This is where nature starts – in the genome. So not to take a genome-centric view is just idiotic to me.

That has to do with philosophy, not with science. But I think there’s a continuum between science and philosophy of how you look at the mechanisms of life.

Ute: Science can only develop in a society that accepts the philosophy of scientific rationality.

Eric: And the society can only obtain a grasp of the part of it which has to do with the biology of life by looking at it the right way. That is, accepting that the properties of living things grow out of the genome. And that that is the basic problem. Every time a physicist decides to turn into a biologist, the worst difficulty he or she has is absorbing

the consequences of genomic information, as opposed to just stresses and pulls and strains and everything else you can think about.

Ute: Many also don't like evolution.

Eric: Many don't like evolution. That's because of the same argument. As soon as you get away from what the genome is doing, you can't understand development, you don't like evolution. And therefore, you're condemning yourself to ignorance of the two most important things that happen in animal life, which is development and evolution. So you can't understand your world.

## **5. The philosophy and success of the causal-mechanistic approach**

Eric It's not just that science can't flourish in a world of people who don't understand that, rather, people can't flourish in a world where they can't understand where animals came from, either in the life cycle or in geological time. They can't understand their own origins, so they either do irrational garbage like pop epigenetics or creationism, or whatever it is, but it's irrational. Understanding development and evolution is the bulwark against an irrational view of life.

Ute: It is so interesting. 100 years ago Jacques Loeb fought against the vitalistic and racist tendencies of his time, saying that mechanistic science is the bulwark against irrationalism, and irrationalism leads to oppression and we have to fight it.

Eric: That's exactly right. But I can be more specific. Appreciating the functions of genomic regulatory information is the bulwark.

Ute: This is a strongly mechanistic approach - looking for causalities in the genes or gene networks. Especially in development, this idea received opposition early on and afterwards. Who are the main opponents?

Eric: There have been a number of different strains of thought in biology which did not really go in this direction, although some of them had to become extinct before one could go further. I think Spemannian thought about development, which is almost like the joke about those guys who are walking around with the sign saying, "food without genes." Spemannian thought is like development without genes. And, of course, it's a dead end. It cannot lead to answers. It can lead to identification of signals, but it always ends in phenomenology. You cannot get to causality except by considering the roots of causality, which are genomic. It's so obvious.

I think that, while I have nothing against modern genetics and it continues to be useful in certain boutique situations, genetics curiously also leads to a kind of causal

phenomenology. You get a mutation and it causes something not to work. It never tells you how it works by itself; you have to do molecular biology. And so, of course, much more gracefully, it is just being supplanted by good, solid molecular regulatory biology. The developmental genetics of 30 years ago is disappearing. I mean, nobody talks about the “awesome power of genetics” like they did in the ‘80s. I got into a big fight with *Nature* once at the end of the 80s. Some stupid editor said, “We only publish articles on the Big Five where you can do genetics.” Yeast (which doesn’t develop), *C. elegans*, *Drosophila*, mouse and I don’t remember what the other was, probably zebrafish. So I refused to have anything to do with them until 2009 or something, when a charming and civilized *Nature* editor came to see me.

Ute: That means you did not publish again in *Nature*?

Eric: I refused to have anything to do with them. I wouldn’t review for them, send anything to them. The Big Five – right – including yeast as a developmental model, because you can do genetics!

Now, I want to ask you, which one of those animals produced a gene network that actually shows you how development works? None of them. The closest we come to it is *Drosophila*, and that’s because people that solved the network started doing regulatory molecular biology and stopped doing genetics on it. And we don’t have very much like that in *Drosophila* except, unfortunately, for 45 minutes of the lifecycle, in the 14 cleavage cycle.

Today, I wouldn’t say gene network developmental biology has outright “enemies” – I don’t think there are enemies; everybody recognizes that this is getting answers – But a lot of people just aren’t interested in the answers that you get. I feel most developmental biologists are at heart still phenomenologists, that’s what turns them on, not causal logic. I think that classical evo-devo, for example, is a hotbed of phenomenology. They really just want to look at how patterns are the same in apparently different animals – They’re romantics, they love to say, “Oh look at that!”

Ute: Are they mainly Germans?

Eric: No. Mostly continental Europeans, though. A lot of Germans, that’s true. They love to show that there’s a hidden similarity in organisms that only look different. It’s completely platonic. But finding things the same doesn’t explain to you anything about where different kinds of animals came from, because if they are different their developmental programs they cannot be the same. What’s different is what’s interesting, not what’s the same. That’s *reductio ad absurdum* in the end.

Ute: Yes, but they are looking for evolutionary relationships.

Eric: They're looking for hidden similarities, but if you take it too far you get the last common ancestor which looks like a baby with antennae and wings and eyeballs and teeth, because if you look from one animal to another you find that certain things in the program to make different body parts are the same from flies to mice. This means the common ancestor was the same. But it actually doesn't mean that. It means something much more subtle.

You asked what the opposition is. The opposition is those who feel that the business of science is to describe, is phenomenology. That's not what I'm interested in. That's not where my science is going. We have to know what the phenomenology is, yes. But I have a favorite saying, that developmental biology for most of my lifetime has been a sea of phenomenology. Elegant, brilliant phenomenology with a few islands of causality floating in it. And now our objective is to completely invert that and make a framework of causality with some islands of phenomenology floating in it.

I think also, hyper-reductionists who don't ever want to look at systems but just want to look at how particular molecules interact or how molecular machines work, are never going to get there either. So it is not, "who is the opposition", it's who's never going to get there.

There is another group who I think do "high tech look-see science", where you just measure everything and then they all think it's all just going to come out in the wash. Or, "why don't you knock out 18,000 genes with CRISPRs [clustered regularly interspaced short palindromic repeats] and we'll find out how everything works." You're not going to find out how everything works. You've got to think about what the meaning of all the circuitry is. You just can't do it that way. You can't get meaning out of directionless, hairball networks of interactions either. So all those things are not going to get there. There are competing approaches to science; that's really what you ask.

Ute: Walter Gilbert predicted in 1991, a decade before the completion of the human genome project, that "The new paradigm, now emerging, is that all the 'genes' will be known (in the sense of being resident in databases available electronically), and that the starting point of a biological investigation will be theoretical. An individual scientist will begin with a theoretical conjecture, only then turning to experiment to follow or test that hypothesis."<sup>1</sup> This would mean that experiments are pushed to the background. What, in your opinion, is the future of experiments?

Eric: In my opinion, before the application of experimental approaches nobody ever learned any science. And after it, in "look-see" science, for example, you're not going to learn any science either. Experiment provides the only way. It's the only way to discover

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<sup>1</sup> <https://cbs.asu.edu/theories-development>



whether an idea operates properly or not. The alternatives you see often in the field of modeling, something I have a lot to do with these days. One of the worst fallacies is the assumption that if you can make a model, which simulates a process, then the model must represent how it works. Physicists claim that this has been their successful approach, but I don't even know if it's true in physics. I have my doubts, but I don't know enough to make a strong argument about it.

But it's clearly not true in biology. The great example is Meinhardt's explanation of *Drosophila* stripes, in terms of reaction-diffusion equations. He explained it perfectly, except it doesn't happen to be how it works. Not partially, rather not at all. Not close. And what showed us how it works, of course, was taking the DNA out and experimentally finding out how it works.

That will always be true. Having a parts list never tells you how anything functions. It's so obvious. If you disassemble an automobile into parts and you didn't know the theory of the internal combustion engine, you would never figure out how that thing works. Just from looking at the discs and nuts and bolts and pieces, you'd never figure it out. Any more than just looking at genes in databases.

Ute: But it is very attractive to do the work on the computer.

Eric: It's worse than that. Why should we pay for this really expensive molecular biology and their endless experiments when if we just invest in big machines that measure everything perfectly, then we'll give it to our bioinformaticians and they will figure it out. But they never will. Sooner or later there has got to be causal experimentation. There has to be perturbation analysis. There is no science that has ever found anything out except by perturbing the system. That's why differential calculus is so important; it looks at changes in things. The only way you ever figure out a process, is by looking at what causes changes. You can't just look at the thing when it's done.

That's why I like to say that you can think that the derivative, in the mathematical sense of evolution, is development. The evolutionary changes that occur in the developmental process are like the first derivative of the phenomenon of evolution. And evolution and development are intimately connected just like that. Evolutionary change means change in developmental process. That's the cause of it. You integrate over the change in the developmental process and you get evolution. So they're not two sciences; they're as connected as those two concepts are in mathematics.

Ute: That's interesting. It reminds of Haeckel but looks like the opposite of him.

Eric: That's not the only thing that's the opposite of Haeckel. That's exactly right. Haeckel was uninterested in process. He was a Platonist. He was certainly –

Ute: A phenomenologist.

Eric: An extreme theoretical phenomenologist.

Ute: In 2011 you were awarded the highly prestigious International Prize for Biology for your pioneering work on developmental gene regulatory networks. Congratulations again. Has your work now become generally accepted?

Eric: One of the things that made me most happy about the Prize was that it was completely devoid of any aspect of representing a medical advance. I think one of the things that has just poisoned biology in our time, all over the world, is the invasion of medical objectives into understanding how life works. Because the practice of medical molecular biology is completely separate from that of doing science. You use the science, we all use engineering, we use it in our lab continuously. But engineering as an objective is not science as an objective. And the pressures that are put on the scientific activity – this is why we have so much scientific fraud, because of the medicalization of the activity.

Ute: I would like to address the problem that all cells of an organism have the same set of genes. As far as I know it took decades after Weismann's suggestion of the opposite to have this idea accepted. Do you remember the discussions?

Eric: Every decade there have been these major battles that had to be fought and that was one of them. In the first decade of my career the biggest battle was about this question, it was that battle. When you look in my '68 book, you can see the discussion of that. It was a very live argument, and Gurdon solved that. But there was a lot of evidence before that.

Ute: In 1958 he cloned the first frog with nuclei from somatic cells; I don't remember which ones.

Eric: It was from gut, actually. It shows that a cell that's already specialized has the capacity in its nucleus to give rise to all the other specialized cells of the animal, which means that every cell has the same genes.

Ute: That leads to another question. The architecture of the cytoplasm – is it also coded in genes?

Eric: Well much of the architecture of cytoplasm is the same from yeast to frogs, and so there's not so much that's particular to – much of basic cell biology is the same in yeast as it is in our cells. For example secretion mechanisms are the same, cell division mechanisms are the same, and chromosome mobilization mechanisms are the same, and so forth. The cell membrane is built the same way; the uptake of materials from outside is the same. Many of the basic processes have nothing particularly animal or developmental

about them. Now when you talk about individual cell types, like neurons and muscle cells and photoreceptor cells, those cell types are very, very ancient in evolution. And they're shared widely across phylogeny.

Ute: But still, how is it transmitted – the information for this architecture. Is it just by division or is it coded?

Eric: It's by transcription.

Ute: But Gurdon needed the egg plasma. He couldn't bring the nucleus to develop anywhere else.

Eric: That's an interesting issue, but it's because most of what's stored in an egg is just a cell biology factory, that's all. An example is the enzymes that make RNA off of DNA. They're all stored in the egg.

Ute: No, not the enzymes, I mean the architecture of the protein scaffolds.

Eric: The reason why you needed an egg is just all that machinery that reads the DNA, which makes protein synthesis. The proteins have to be made. It's just machinery, not much architecture is required.

So, for instance, as we heard in one of the symposia, you had a very interesting guy from Venter's group [John Glass] about making an artificial bacteria from DNA. So, really, all that's needed outside of the DNA is a transcription system that can start to read the DNA. And if you give it that, and give it a little boost, then it will make the ribosomes and make the protein synthesis machinery, and then it will transcribe and make all the things it needs. But that's what's really in the egg - just machinery. Cell biology machinery.

Ute: This they were not able yet to do artificially -

Eric: Can't do it yet, but they will soon. There's no reason it won't work.

You know, Gurdon wasn't trying to do anything except address that particular question, which he did successfully do. Then he did it over again, and over again, and over again, locking up every little loophole. And when he did that experiment, people didn't realize that the gut has stem cells in it which are not actually differentiated. But he carefully showed, just in case, because he's a really good scientist, that the cells that gave the nuclei, that gave the whole organism, were actually differentiated gut cells. We didn't even know stem cells existed, but he showed the donor cells were differentiated. So that obviates that. But that was the great battle of the '60s. That and the Variable Gene Activity theory, so to speak. We would call it transcription control theory of differentiation.

But differentiation and making an embryo are not the same thing, of course. You've got all the spatial gene expression that has to be set up. A very abstract patterning process, and nobody appreciated it. It's been a fascinating ride, I can tell you that.

Ute: It is fascinating. Also the disputes. And it is one of the fields in which philosophical reasoning has played a major role.

Eric: The number of issues obscures the fact that there actually are not multiple ways of thinking about causality in development and evolution. There's only one way.

Ute: That's what you say!

Eric: But it happens to be true. And that's very hard for people to take who don't know that way. But today, we say there's only one way to think about many aspects of physics; it wasn't always so. But there is such a thing as THE correct scientific answer about nature.

Ute: Yes, there is a lot of change and errors. Dead-ends and whatever, but there is also something –

Eric: There is something about the world and the way it is and the way it works. That's exactly right.

Ute: And that's sometimes underestimated.

Eric: So you can't say, that's what I say. I say that that's what the experiments show.

Ute: Thank you very much for sharing your most interesting views with me!

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